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MICROGLIAL RAC1 DRIVES EXPERIENCE-DEPENDENT BRAIN PLASTICITY

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Abstract:
Microglia, the immune defenders of the brain, continuously extend and retract their processes to sense and decipher their local environment. This includes interactions with synapses to maintain brain homeostasis. To do this, microglia rely on the actin cytoskeleton and subsequent intracellular signaling, which is adapted in response to external signals released by cells undergoing intense synaptic activity. Thus, proteins that regulate actin cytoskeleton dynamics, intracellular trafficking, and integration of extracellular signaling, such as RhoA, Rac1 and Cdc42 from the Rho GTPase family, are good candidates to govern microglial sensing capacity and homeostasis. In this study, using conditional cell-specific gene targeting in mice combined with multi-omics approaches, immunofluorescence, and behavioral tests we aimed to identify the roles of Rho GTPase Rac1 in microglia homeostasis. We demonstrate that the Rho GTPase Rac1 is essential for microglia to sense and interpret their local microenvironment. This impacts the microglia-synapse crosstalk that is required for experience-dependent plasticity, a fundamental brain property impaired in several neuropsychiatric disorders. Furthermore, phosphoproteomics profiling of microglia isolated from mice exposed to an environmental enrichment protocol (known to induce experience-dependent synaptic plasticity and cognitive performance) detects a large modulation of Rho GTPase signaling, predominantly of Rac1. Additionally, our results show that environmental enrichment likely requires tight regulation of Rho GTPase-dependent pathways. Ablation of

microglial Rac1 affected pathways involved in microglia-synapse communication, disrupted experience-dependent synaptic remodeling and blocked the gains in learning, memory, and sociability induced by environmental enrichment. Overall, our results place microglial Rac1 as a central regulator of pathways involved in the microglia-synapse crosstalk required for experience-dependent synaptic plasticity and cognitive performance, suggesting that modulation of Rho GTPase signaling in microglia might be a useful strategy to boost neuroplasticity in health and disease.
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